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Fertility and gonadal function in female survivors after treatment of early unfavorable Hodgkin lymphoma (HL) within the German Hodgkin Study Group HD14 trial

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Background: In the HD14 trial, 2× BEACOPP_{escalated} + 2× ABVD (2 + 2) has improved the primary outcome. Compared with 4× ABVD, this benefit might be compromised by more infertility in women. Therefore, we analyzed gonadal function and fertility.

Patients and methods: Women ≤45 years in ongoing remission at least 1 year after therapy were included. Hormone parameters, menopausal symptoms, measures to preserve fertility, menstrual cycle, pregnancies, and offspring were evaluated.

Results: Three hundred and thirty one of 579 women addressed participated (57.2%) and 263 per-protocol treated patients qualified (A = ABVD: 137, B = 2 + 2: 126, mean time after therapy 42 and 43 months, respectively). Regular menstrual cycle after treatment (A: 87%, B: 83%) and time to recovery (≤12 months) were not different. Follicle-stimulating hormone and anti-Müllerian hormone were significantly better in arm A. However, pregnancies after therapy favored arm B (A: 15%, B: 26%, *P* = 0.043) and motherhood rates were equivalent to the German normal population. Multivariate analysis revealed prophylactic use of gonadotropin-releasing hormone (GnRH) analogues as highly significant prognostic factor for preservation of fertility (odds ratio = 12.87, *P* = 0.001). Severe menopausal symptoms were frequent in women ≥30 years (A: 21%, B: 25%).

Conclusions: Hormonal levels after 2 + 2 indicate a reduced ovarian reserve. However, 2 + 2 in combination with GnRH analogues does not compromise fertility within the evaluated observation time.

Key words: chemotherapy, fertility, GnRH analogues, Hodgkin lymphoma, ovarian reserve

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introduction

Hodgkin lymphoma (HL) has become a curable malignancy over past decades. The disease is usually treated with a combination of chemotherapy and involved-field radiotherapy (IFRT). With progression-free survival rates ~87% in early unfavorable stages, there are many long-term survivors, most of them of young age [1, 2]. Thus, there is a need to analyze long-term side-effects and to carefully consider the risk to benefit ratio of established as well as of newly introduced treatment regimens. Among these treatment-related toxic effects, gonadal dysfunction and infertility are especially relevant because they affect the quality of many life-years [3].

The problem of gonadal dysfunction is more pronounced in women than in men for two reasons. First, chemotherapy can result in gonadal dysfunction and impaired spermatogenesis (exocrine hypogonadism) but usually does not lead to clinically significant endocrine hypogonadism with normal testosterone levels in most men [4]. In contrast, female gonadal dysfunction after chemotherapy often includes endocrine hypogonadism and premature ovarian failure [5]. Both are compromising quality of life and can cause medical problems such as osteoporosis and long-term cardiovascular disease [6]. Secondly, preservation of fertility is much easier and more established in men than in women: semen analysis and cryopreservation of sperm are a standard procedure before chemotherapy. For established fertility preservation techniques in women, time and a partner are needed and the cryopreservation of oocytes or ovarian tissue is more invasive and still does not yield satisfactory results [7].

It has been shown for both male and female patients that the rate of treatment-induced infertility increases with more aggressive chemotherapy [4, 8, 9]. Alkylating agents, especially procarbazine and cyclophosphamide, have a strong negative impact on fertility. These drugs are included in the BEACOPP regimen (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone) that had mainly been used in advanced-stage HL. In contrast, ABVD (adriamycin, bleomycin, vinblastine, dacarbazine), the standard of care for early-stage HL, is regarded less gonadotoxic [10–12].

In the German Hodgkin Study Group (GHSG) HD14 study, escalation of chemotherapy using 2× BEACOPP_{escalated} + 2× ABVD (arm B, 2+2) compared with 4× ABVD (arm A) provides a better outcome with an estimated 4-year freedom from treatment failure rate of 94.7% compared with 89.3% [13]. However, this improved tumor control must be carefully balanced against the presumed negative long-term toxicity such as infertility or gonadal dysfunction. The main objective of the present analysis was therefore to assess gonadal function and fertility in female survivors treated with the new 2 + 2 regimen as compared with four cycles of ABVD.

patients and methods

HD 14 trial: patients and study design

Patients between the age of 18 and 60 with biopsy-proven HL of clinical stages IA, IB, IIA or IIB with at least one of the following risk factors were

included: bulky mediastinal mass ($\geq 1/3$ maximum transverse thorax diameter), extranodal involvement, erythrocyte sedimentation rate ≥ 50 mm/h (or ≥ 30 mm/h in patients with 'B' symptoms), or three or more lymph node areas involved. Patients with stage IIB disease and bulky mediastinal mass and/or extranodal involvement were not included. Patients with impaired heart, lung, liver, or kidney function; previous malignant disease, or HIV-positive status were excluded. Patients were also excluded if they were pregnant or lactating. The study was carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice (ICH-GCP). Randomization was carried out at the GSHG central trial office into treatment arms A (four cycles of ABVD) or B (two cycles of BEACOPP_{escalated} plus two cycles of ABVD). Chemotherapy was followed by standard 30 Gy IFRT.

assessment of gonadal function and fertility

Gonadal function and fertility after treatment were evaluated by contacting all female patients (18–40 years at time of randomization) in ongoing remission at least 1 year after therapy and without any other chemotherapy treatment than the HD14 study medication (i.e. exclusion of relapsed patients). Patients had to have signed written informed consent that allowed us to address them for questions related to their initial treatment.

questionnaires

Menopausal symptoms were determined using the Menopause Rating Scale (MRS) [14, 15]. Additional questions referred to the use of hormonal substitution, methods of fertility preservation before therapy, menstrual status, pregnancies and offspring, hormonal analyses, and social aspects. Additionally applied, but not reported here, were quality-of-life assessments using the QLQ-C30 questionnaire [16].

hormonal analysis

Patients were asked to take a blood sample at the end of the pill break or at day 3 of a new menstrual cycle and to send them to us for analysis of hormones. Blood samples were then processed and stored at -20°C until analysis. Endocrine screening included standardized serum assays for follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol [heterogenic, noncompetitive chemiluminescent immunometric assays, Elecsys-LH, Elecsys-FSH, Elecsys-Estradiol-II (Roche Diagnostics GmbH, Mannheim, Germany)], and anti-Muellerian hormone (AMH) [active AMH Gen II ELISA (Beckman Coulter Company, Praha, Czech Republic)].

statistics

To allow conclusive analysis of treatment consequences, we analyzed only per-protocol treated patients of the HD14 study. The main analysis set included females ≤ 40 years at first diagnosis of HL and ≤ 45 years at time of fertility assessment who were survivors in ongoing remission at least 1 year after therapy. A further analysis set was used for multivariate prediction of pregnancies. For this analysis set, only women taking no hormonal contraceptives at time of assessment and having a male partner for sexual intercourse were included (core set). As age is a crucial factor for fertility, most results are separately reported for survivors in age groups of 18–29 years and 30–45 years.

Outcome measures of fertility were pregnancies after therapy (primary outcome measure), other direct indicators (regular cycle, time to regular cycle), hormonal parameters (FSH, AMH, LH, estradiol), and menopausal symptoms (MRS). Hormonal parameters were natural log transformed before statistical computations to normalize distributions.

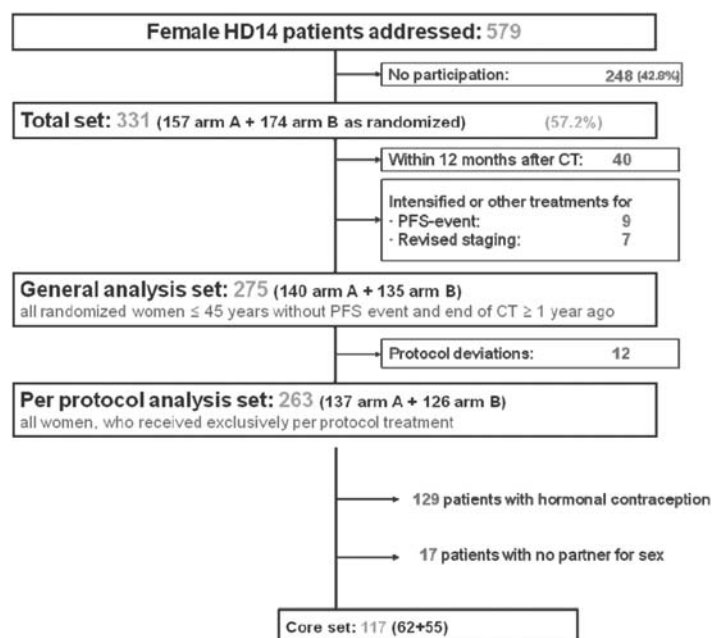


Figure 1. Consort chart. CT, chemotherapy; PFS, progression-free survival.

Table 1. Patient characteristics

		Per protocol				Total set	
		Participating		Not participating		Participating	Not participating
		4× ABVD	2 + 2	4× ABVD	2 + 2		
N		137	126	142	154	331	230
Age at fertility assessment	y	32 ± 7 (20–45)	32 ± 7 (20–44)	n.a.	n.a.	32 ± 7 (20–45)	n.a.
Age at HL diagnosis	y	28 ± 7 (18–39)	28 ± 7 (18–39)	27 ± 7 (18–39)	28 ± 6 (18–39)	28 ± 7 (18–39)	27 ± 7 (18–39)
Treatment duration	w	15 ± 1 (11–21)	13 ± 1 (11–17)	15 ± 2 (2–21)	13 ± 2 (5–23)	14 ± 3 (2–23)	14 ± 2 (2–23)
Time from end of CT	m	42 ± 20 (12–83)	43 ± 19 (12–77)	n.a.	n.a.	39 ± 22 (12–83)	n.a.
Ann Arbor Stage	1A	3 (2%)	1 (1%)	2 (1%)	3 (2%)	5 (2%)	4 (2%)
	1B	3 (2%)	2 (2%)	1 (1%)	4 (3%)	6 (2%)	4 (2%)
	2A	105 (77%)	101 (80%)	104 (74%)	101 (80%)	236 (78%)	175 (76%)
	2B	26 (19%)	22 (18%)	33 (24%)	19 (15%)	54 (18%)	46 (20%)
B symptoms	yes	31 (23%)	25 (20%)	32 (23%)	26 (21%)	64 (21%)	50 (22%)
Large mediastinal mass	yes	30 (22%)	32 (25%)	35 (25%)	34 (27%)	73 (24%)	58 (25%)
Extranodal involvement	yes	13 (10%)	10 (8%)	9 (6%)	13 (10%)	32 (11%)	13 (6%)
≥3 nodes	yes	98 (72%)	87 (69%)	92 (66%)	95 (75%)	210 (70%)	162 (71%)
High ESR	yes	69 (50%)	67 (53%)	74 (53%)	70 (56%)	158 (53%)	122 (53%)
IPS	0–1	112 (87%)	102 (86%)	108 (82%)	100 (85%)	247 (87%)	175 (83%)
	2–3	17 (13%)	16 (14%)	23 (18%)	18 (15%)	37 (13%)	37 (18%)
Motherhood before	yes	54 (41%)	41 (35%)	41 (35%)	44 (33%)	114 (37%)	66 (34%)
Pill	yes	45 (34%)	41 (33%)	n.a.	n.a.	103 (32%)	n.a.
GnRH	yes	25 (19%)	36 (29%)	n.a.	n.a.	78 (24%)	n.a.
Contraception now	yes	64 (49%)	65 (52%)	n.a.	n.a.	158 (49%)	n.a.
Sex partner now	yes	117 (89%)	113 (90%)	n.a.	n.a.	287 (89%)	n.a.

Continuous data: mean ± standard deviations (range), categorical data: frequencies (percent of valid answers).

CT, chemotherapy; ESR, erythrocyte sedimentation rate; GnRH, gonadotropin-releasing hormone; HL, Hodgkin lymphoma; m, months; n.a., not available because information requires participation; w, weeks; y, years.

To evaluate effects of age, motherhood before therapy, time since end of chemotherapy, use of gonadotropin-releasing hormone (GnRH) analogues, oral contraception, and treatment on pregnancies, a logistic regression in

the core set was computed. Recent data on motherhood in Germany were used to compare motherhood rates of our treatment groups with representative reference data in five age groups.

The level of significance was set to 0.05 two-sided. Continuous parameters were tested with *t*-test for independent groups, categorical data with binomial test, and no corrections for multiple testing were applied. All statistical analyses were computed with Statistical Analysis System release 9.2. (SAS Institute, Cary, NC).

results

patient characteristics

A total of 331 (57.2%) of 579 contacted women participated (arm A: 157, arm B: 174). After excluding patients being less than first 12 months after therapy or those with additional therapy or protocol deviations, the per-protocol analysis set included 263 women (arm A: 137, arm B: 126). For the multivariate analysis of predictors of fertility, only women without contraception and reporting sexual intercourse were included, resulting in a core set of 117 patients (arm A: 62, arm B: 55; Figure 1).

Comparison of the per-protocol analysis set and the entire HD14 cohort showed no relevant differences in terms of patient, treatment, or lymphoma characteristics (Table 1). Mean age at fertility assessment was 32 years in both arms and mean observation time from end of treatment was 42 months in arm A and 43 months in arm B. All patient characteristics were well balanced between the two treatment groups except for the use of GnRH analogues during chemotherapy which were given more frequently in the 2 + 2 group (29%) compared with those treated with 4× ABVD (19% Table 1).

hormonal analysis

Serum levels of AMH and FSH were different between the treatment arms. These differences in favor of ABVD were high and significant for FSH in older women (30–45 years at assessment: arm A: 4.4 U/l, arm B: 11.9 U/l) and for AMH in both age groups (18–29 years at assessment: arm A: 2.2 µg/l, arm B: 0.9 µg/l; 30–45 years at assessment: arm A: 0.8 µg/l, arm B: 0.03 µg/l) (Table 2).

menopausal symptoms

There was no significant difference between treatment arms in menopausal symptoms as measured by MRS total score. The same is true for any of the subdimensions of the MRS (urogenital, psychological and somato-vegetative; data not shown). However, both arms showed an age-related increase of menopausal symptoms and more severe symptoms than in a 45- to 60-year-old German reference cohort (Table 2) [14].

menstrual status

Over 90% of the patients ≤30 years reported a regular cycle with no difference between treatment arms. In the older group, 84% in arm A had a regular cycle compared with 74% in arm B. This difference was not significant (Table 2).

The time to regular menstrual cycle after therapy was almost equal between treatment arms. With very rare exceptions, recovery of regular menstrual cycle was completed within 12 months. The use of GnRH analogues during therapy deferred recovery of a regular cycle for ~1 month (Figure 2a and b).

Table 2. Fertility parameters of per-protocol treated survivors in two age groups and for the two treatment arms (A: 4× ABVD, B: 2× BEACOPP_{escalated} + 2× ABVD)

	18–29 years				30–45 years			
	N valid	A ^a	B ^a	A–B ^a	N valid	A ^a	B ^a	A–B ^a
	A, B	48	58	106	A, B	89	68	157
Hormones ^b								
AMH [µg/l] ^b	48, 58	2.2	0.9	+1.3***	88, 68	0.8	0.03	+0.8***
FSH [U/l] ^b	46, 55	3.0	4.3	–1.3	88, 67	4.4	11.9	–7.5***
Menopausal symptoms (MRS, total score)								
MRS total score	38, 45	7.3	6.5	+0.8	67, 52	9.1	9.6	–0.5
MRS severity ^c	38, 45				67, 52			
Severe (8%) ^c		16%	7%	+9%		21%	25%	–4%
Moderate (20%) ^c		16%	22%	–6%		19%	17%	+2%
Mild (25%) ^c		32%	22%	+10%		30%	29%	+1%
No/few (48%) ^c		37%	49%	–12%		30%	29%	+1%
Patient reported events after HL therapy								
Regular Cycle after therapy	46, 55	100%	100%	0%	83, 68	94%	90%	+4%
Regular Cycle presently	46, 57	91%	95%	–3%	83, 68	84%	74%	+11%
Pregnancy	47, 55	13%	22%	–9%	83, 67	17%	30%	–13%
Birth	41, 45	12%	13%	–1%	77, 58	12%	28%	–16%*

Bold values are statistically significant.

Arithmetic means and *t*-tests for continuous variables, relative frequencies in percent and binomial tests for categorical data.

All computations for AMH and FSH with log-transformed values to normalize distributions; table entries in original units (after exponentiation).

Classification of MRS total score with reference scores for 45- to 60-year-old German females in parentheses.

****P* ≤ 0.001, **P* ≤ 0.05.

AMH, anti-Muellerian hormone; FSH, follicle-stimulating hormone; MRS, Menopause Rating Scale.

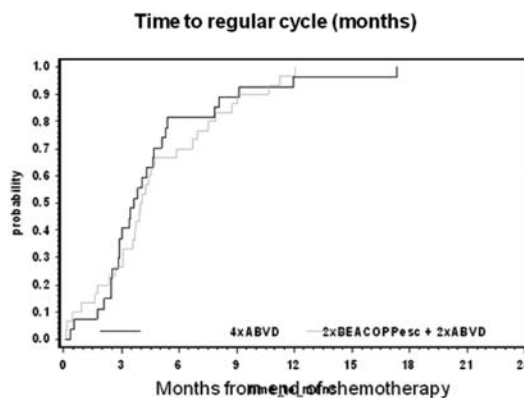
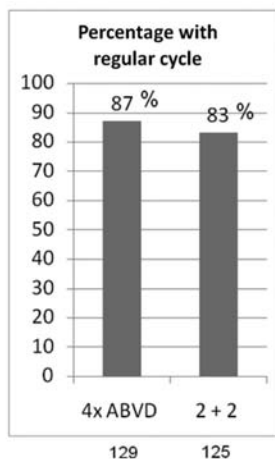
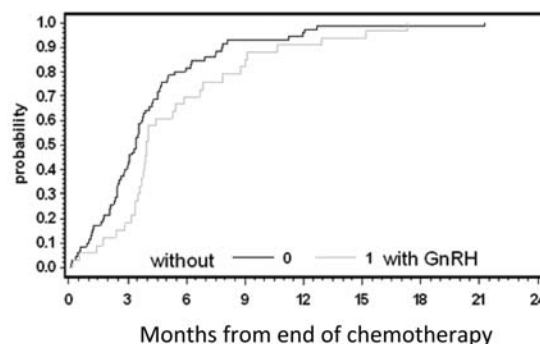
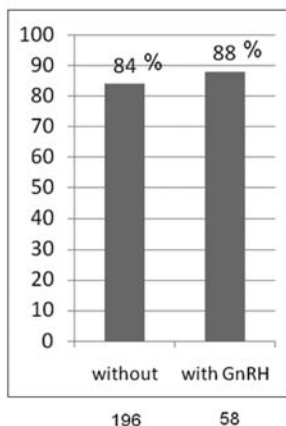
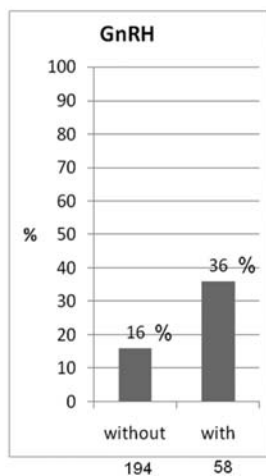
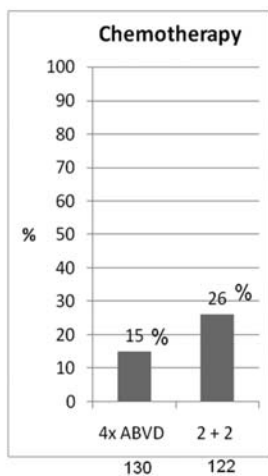
A Chemotherapy**B GnRH****C Pregnancies**

Figure 2. Percent of survivors with regular cycle and time to regular cycle for (A) chemotherapy regimen and (B) GnRH.

pregnancies and motherhood

In summary, 20 patients in arm A (15%) reported a pregnancy compared with 32 patients (26%) in arm B (supplemental Figure S1, available at *Annals of Oncology* online). The difference was significant ($P = 0.043$) favoring the more

aggressive arm B (2 + 2). Logistic regression analysis of potential contributing factors in the core set (Table 3) showed that motherhood before therapy, age, treatment arm, and oral hormonal contraception during therapy did not significantly predict pregnancies (all $P > 0.10$). However, the use of GnRH

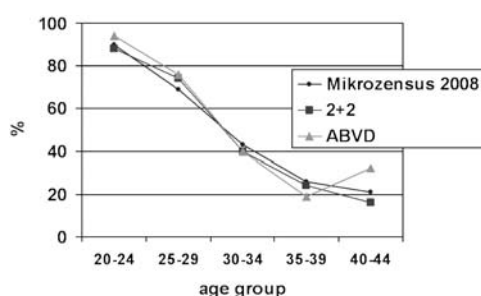
Table 3. Logistic regression for prediction of pregnancies after end of CT in core set ($N = 117$)

	OR	P
Before therapy		
Motherhood	0.82	0.76
Therapy		
ABVD versus 2 + 2	0.50	0.18
Pill	1.64	0.43
GnRH	12.87	0.0010
After care		
Months since CT	1.07^a	0.0008
Age	0.96 ^a	0.50
N	109	
df	6	
P	<0.0001	

Bold values are statistically significant.

Continuous variable: OR depends on unit of measurement risk relation for every increase of 1 month or year.

CT, chemotherapy; GnRH, gonadotropin-releasing hormone; OR, odds ratio.

**Figure 3.** Percentage of childless women in five age groups compared with representative statistics of the German general population.

analogues during chemotherapy [odds ratio (OR) = 12.87, $P = 0.0010$] and the time after chemotherapy ($P = 0.0008$) significantly increased the probability to become pregnant. The motherhood rates of the main analysis set in five different age groups were comparable to representative data of the German general population (Figure 3) [17].

influence of GnRH analogues and pregnancies on hormones

AMH was not sensitive to application of GnRH analogues during therapy or pregnancies after therapy (core set, $P = 0.46$ and $p = 0.95$). Conversely, FSH differed significantly between the two groups with and without pregnancy ($P < 0.0001$) and differed to some degree between the two GnRH groups ($P = 0.14$).

discussion

This study investigated gonadal function and fertility of 263 female HL patients treated within the GHSG trial HD14 for early unfavorable disease. The following major findings emerge from this analysis: First, female fertility, defined as pregnancies after therapy, is not compromised after two cycles of

BEACOPP_{escalated} in the 2 + 2 regimen as compared with ABVD only. In addition, motherhood rates in five different age groups of our study are equivalent to the respective motherhood rates of the general German female population indicating no impairment of fertility at all. Accordingly, a regular menstrual cycle was reported by most women in both arms (arm A: 87%, arm B: 83%) and recovery occurred within 1 year after therapy. Secondly, the prophylactic use of GnRH analogues during therapy was followed by significantly more pregnancies after therapy. Thirdly, serum levels of AMH did not correlate with the use of GnRH analogues. Fourthly, hormonal levels of AMH and FSH demonstrate a distinct difference between both treatment arms in favor of ABVD. Fifthly, compared with 4× ABVD women do not report more menopausal symptoms after the BEACOPP_{escalated} containing regimen (2 + 2). In both arms relevantly more females suffer from severe menopausal symptoms than expected for a considerably older reference cohort.

This is the largest study in a uniformly treated and well-defined patient population on gonadal function and fertility after chemotherapy. Nonetheless, with regard to female gonadal function determined by hormonal serum levels, our results need to be interpreted with caution. The analysis was carried out after the reported pregnancies and serum samples were collected locally under non-standardized conditions and might not be reliable [18]. In addition, a transvaginal ultrasound to determine the antral follicle count was not carried out in our patients [19]. However, we included also AMH in our analysis, i.e. known to be independent of the menstrual cycle, and is widely discussed as a valuable predictor of ovarian reserve and reproductive function [19–23].

Though we observed significant differences in serum AMH levels especially in younger women treated with ABVD, there were more pregnancies in the 2 + 2 arm. Thus, AMH levels were not conclusive on female fertility in our data. However, as decreased AMH levels indicate a reduced follicle pool, we cannot exclude a higher rate of future POF [24]. A longer follow-up period is needed to proof this potential effect. Since POF should be accompanied by menopausal symptoms, we also investigated this issue in our cohort and compared the results to a representative sample of German women aged between 45 and 60 years [14]. This is the best matching control cohort for our analysis as MRS reference scores for younger women are not available. However, already above the age of 30 years, the rate of females suffering from severe menopausal symptoms in our study is approximately threefold higher than in the control cohort. This is true for both regimens and emphasizes the urgent need for a comprehensive aftercare of young women after HL.

Finally, amenorrhea has been widely used as an indirect indicator of gonadal dysfunction after cancer treatment though regular menstrual period does not necessarily represent an ovulation [5, 9]. In our study cohort, most women reported a regular cycle after therapy, again without significant differences between the treatment arms. Interestingly, almost no woman reported recovery of the menstrual cycle beyond 1 year after therapy. Thus, our data suggest referring women without a regular cycle later than 1 year after therapy and desire for children to a center for reproductive medicine.

Obviously, apart from any hormonal serum levels, infertility is the most relevant end point for female HL patients. Infertility is hard to assess as primary end point in clinical studies as the inability to conceive or give birth to a child is a time-dependent parameter. It is, therefore, difficult to diagnose and evaluate at a given time point. Nevertheless, the most valid end points for fertility remain the number of pregnancies and offspring. Unfortunately, only some authors have reported the number of childbirths after HL therapy, often in small noncontrolled series [5, 25, 26].

In our study, we observed normal motherhood rates for patients treated with ABVD and the 2 + 2 regimen that included the more aggressive BEACOPP_{escalated} chemotherapy. Even after adjusting for the use of GnRH analogues in the logistic regression analysis, there was no evidence for impaired fertility after the 2 + 2 regimen within the evaluated observation time. This result is even more impressive taking into account that relapsed HL patients were excluded from analysis. Relapses occurred more often after ABVD and were usually treated with high-dose chemotherapy causing infertility in almost all cases. Thus, in this respect, the current analysis has a small bias in favor of 4× ABVD.

Despite some methodological limitations of our study, the investigated cohort is large and the majority of HD14 patients participated in the survey. In addition, all patients were uniformly treated with two well-defined regimens. With the notable exception of GnRH application during treatment, patient characteristics were well balanced between arms and were representative for all female survivors.

The prophylactic use of GnRH analogues for ovary protection during cancer treatment is subject of controversial discussions. It has been investigated in few prospective randomized studies with contradictory results. Three of these trials using surrogate parameters showed no protective effect of GnRH analogues and two were positive [27–31].

A retrospective study with a more comprehensive approach including transvaginal ultrasound, found no benefit for GnRH analogues in terms of ovarian function [32]. However, the multivariate analysis in the present study reveals that the use of GnRH analogues during therapy is a strong, independent, and a highly significant predictor of pregnancies. Of course, only prospective randomized studies could definitely confirm a causal relationship between use of GnRH analogues and preservation of fertility in the unfavorable early stages of HL. An important confounder in this retrospective analysis might be the patient's strong wish to preserve fertility resulting in a more frequent use of GnRH analogues as compared with women not expressing this desire. To minimize this effect, we excluded those women from the multivariate analysis who had no sexual partner or who used any contraception after therapy (core set). In addition, we included possible confounders into the analysis as motherhood before therapy and oral contraception during therapy. We thereby adjusted our analysis to a high degree and nevertheless found surprisingly strong (OR > 12) indirect evidence supporting the prophylactic use of GnRH analogues in women receiving therapy for early unfavorable HL.

In summary, 2× BEACOPP_{escalated} followed by 2× ABVD has a stronger impact on ovarian reserve, reflected by reduced

AMH and increased FSH serum levels. However, we cannot find any notable differences between the treatment arms in terms of the clinically valid end points amenorrhea, menopausal symptoms, pregnancies, or offspring. Thus, treatment of early unfavorable HL in young women with the effective combination of 2× BEACOPP_{escalated} followed by 2× ABVD and IF-RT has only a subclinical impact on ovarian function but—within the evaluated observation time—not on fertility itself, especially when combined with the prophylactic use of GnRH analogues. This result must be taken into account when judging the overall benefit of the 2 + 2 regimen for female early unfavorable HL patients.

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disclosure

The authors declare no conflicts of interest.

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Adding docetaxel to cisplatin and fluorouracil in patients with unresectable head and neck cancer: a cost–utility analysis

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Background: Adding docetaxel (Taxotere, T) to induction chemotherapy with platinum/infusional 5-FU (PF) has been shown to improve overall survival of patients with head and neck cancer. The aim of the study was to analyze the cost–utility of TPF in patients with unresectable disease.

Design: We developed a Markov model to represent patient's weekly transitions among different health states, related to treatment or disease status. Transition probabilities were obtained from the TAX 324 clinical trial report and from the

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